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L8: Entry 28 of 142 File: PGPB Jul 4, 2002

DOCUMENT-IDENTIFIER: US 20020086896 A1
TITLE: Therapeutic inhibitor of vascular smooth muscle cells

Summary of Invention Paragraph (14):
[0013] Thus, the invention further provides a method for inhibiting or reducing diminution in vessel lumen volume in a traumatized mammalian blood vessel. The method comprises administering to the blood vessel of a mammal an effective amount of cytoskeletal inhibitor, wherein the cytoskeletal inhibitor is in substantially crystalline form and wherein the crystals are of a size which results in sustained release of the cytoskeletal inhibitor. Preferably, the crystals are of a size of about 0.1 micron to about 10 mm, preferably about 1 micron to about 25 micron, in size. Methods to determine the size of crystals useful for sustained release are well known to the art. Preferably, the cytoskeletal inhibitor is administered in situ, by means of an implantable device, wherein the cytoskeletal inhibitor is releasably embedded in, coated on, or embedded in and coated on, the implantable device. Preferably, the crystalline cytoskeletal inhibitor is releasably embedded in, or dispersed in, a adventitial wrap, e.g., a silicone membrane. For example, a preferred therapeutic implantable device of the invention comprises about 5 to about 70, preferably about 7 to about 50, and more preferably about 10 to about 30, weight percent of a cytochalasin, e.g., cytochalasin B or an analog thereof, per weight percent of the adventitial wrap. Another preferred therapeutic implantable device of the invention comprises about 1 to about 70, preferably about 2 to about 50, and more preferably about 3 to about 10, weight percent of taxol or an analog thereof per weight percent of the adventitial wrap. Alternatively, a preferred therapeutic implantable device of the invention comprises about 35 to about 70, preferably about 35 to about 60, and more preferably about 35 to about 50, weight percent of taxol or an analog thereof per weight percent of the adventitial wrap.

Detail Description Paragraph (140):
[0185] The therapeutic agents and dosage forms of the invention are useful to treat or inhibit a diminution in vessel lumen volume, area and/or diameter associated with a procedural vascular trauma. A vascular trauma includes but is not limited to trauma associated with an interventional procedure, such as angioplasty, placement of a stent, shunt, stet, synthetic or natural graft, adventitial wrap, indwelling catheter or other implantable devices. Grafts include synthetic therapeutic agent-treated grafts, e.g., impregnated or coated grafts. As used herein, "vessels" includes mammalian vessels, e.g., coronary vessels as well as peripheral, femoral and carotid vessels. It will be recognized that the therapeutic agents and dosage forms (both free and sustained release) of the invention are not restricted in use for therapy following angioplasty; rather, the usefulness of the therapeutic agents and dosage forms will be proscribed by their ability to inhibit cellular activities of smooth muscle cells and pericytes in the vascular wall. Thus, other aspects of the invention include therapeutic conjugates and dosage forms and protocols useful in early therapeutic intervention for reducing, delaying, or eliminating (and even reversing) atherosclerotic plaques and areas of vascular wall hypertrophy and/or hyperplasia.

Detail Description Paragraph (414):
[0392] Swine coronary arteries were also traumatized by embolectomy or over-sized PTCA balloon, and then 8-16 ml of cytochalasin B at 8.0 .mu.g/ml was infused into the arterial wall with a MIC catheter to achieve a therapeutic dose. Controls included a diluent control and a traumatized untreated control, and all animals were sacrificed 4 weeks after intervention and coronary arteries were fixed by perfusion. Morphometry was performed on selected sections from proximal, treated and distal segments of coronary arteries (Table 15).

L8: Entry 76 of 142 File: USPT Dec 4, 2001

DOCUMENT-IDENTIFIER: US 6326017 B1
TITLE: Methods for the localized delivery of agents to blood vessels

Brief Summary Text (23):
Localized delivery of an agent to a blood vessel by the methods of the present invention is achieved by applying a carrier containing at least one agent to an external ("adventitial") surface of a blood vessel and isolating the agent, or agents, from the adjacent tissue. An agent may act on a wall or the lumen of a blood vessel. The blood vessel to which an agent is applied may be an artery or a vein. A preferred blood vessel is an artery or vein undergoing anastomosis. A preferred artery is an artery undergoing endarterectomy, such as a carotid, aorta or femoral artery. The carrier may be applied to the entire circumference of a blood vessel or to a portion thereof. Similarly, the portion of the length of blood vessel to which an agent is applied will be evident to one skilled in the art depending upon the particular circumstances.

Detailed Description Text (5):
Thirty minutes after application of the PVA, both common carotid arteries were occluded by microclips at the proximal and distal ends of the segment with injured endothelium. After 1 hour of occlusion, the systemic prothrombin time (PT) and partial thromboplastin time (PTT) were determined from arterial blood drawn from a femoral catheter. The microclips were then removed, and blood flow was established again in both carotid arteries for 5 minutes. Vessels were perfusion-fixed in situ at physiologic pressure (mean 80 mm Hg) with intracardiac 0.12 M phosphate buffer (pH 7.4) followed by 4% paraformaldehyde and 1% glutaraldehyde in buffer. The common carotid arteries were removed and placed in 1.5% glutaraldehyde/buffer overnight.

Detailed Description Text (17):
Thirty adult male Sprague-Dawley rats weighing 450-500 gm were anesthetized with sodium pentobarbital (50 mg/kg intraperitoneally) after the administration of atropine sulfate (0.05 mg/kg intramuscularly). The left common, external and internal carotid arteries were exposed in the neck through a midline incision, and a 2-French balloon embolectomy catheter introduced into the external carotid artery. The catheter was positioned in the proximal common carotid artery (CCA), then inflated and withdrawn three times to produce a consistent 2 cm segment of endothelial desquamation. Four hundred units (0.02 ml, 20,000 .mu./ml) of heparin sulfate (Organon, Inc.; West Orange, N.J.) was mixed with 0.04 ml of polyvinyl alcohol (PVA) (Elvanol, Du Pont Corp., Wilmington, Del.; 16% weight: volume in water) to produce a viscous gel. Using sterile technique, the heparin/PVA gel was applied immediately after mixing to the adventitial surface of the de-endothelialized CCA, and surrounded by a silastic shell to prevent release into adjacent tissue. In control rats, PVA without heparin (0.06 ml) was similarly applied to the de-endothelialized left CCA. Animals in both groups were sacrificed at 5 (N=10), 10 (N=10) and 20 (N=10) days after endothelial injury by perfusion-fixation at physiologic pressure (mean 80 mmHg) with 100 ml intracardiac 0.12 M phosphate buffer (PB;pH 7.4) followed by 200 ml of 4% paraformaldehyde and 1% glutaraldehyde in PB. Fifteen minutes before sacrifice, Evans blue dye (Sigma, St. Louis; 60 mg/kg in phosphate buffered saline, pH 7.4) was injected via a left femoral catheter. In animals from groups at 5 and 10 days after endothelial injury, 2.7 ml of femoral venous blood was collected prior to sacrifice for systemic prothrombin time (PT) and partial thromboplastin time (PTT). Additionally, animals in the 5 day group had PT and PTT determinations from femoral venous samples drawn at 1 day after injury.

Detailed Description Text (18):
After perfusion-fixation, 10 mm segments of left CCA were removed, placed in 1.5% glutaraldehyde/PB overnight, then divided into two 5 mm segments for light

microscopy/immunohistochemistry and scanning electron microscopy (SEM), respectively. The distal 5 mm segment of the CCA for SEM was placed in buffered 1% osmium tetroxide, dehydrated in graded ethanols, and critical-point dried. The luminal surface was exposed after mounting, coated with gold, and examined and photographed with a JEOL scanning electron microscope (Peabody, Mass.).

L8: Entry 117 of 142 File: USPT Feb 10, 1998

DOCUMENT-IDENTIFIER: US 5716340 A
TITLE: Blood perfusion catheter

Abstract Text (1):
A blood perfusion balloon catheter is provided. The perfusion catheter includes an elongate tubular shaft having a proximal portion and a distal portion and a plurality of toroidal-shaped inflatable balloons laced through the distal portion of the tubular shaft, the balloons creating a blood flow lumen when they are inflated. The perfusion catheter may also include a cylindrical sheath attached to the balloons.

Brief Summary Text (17):
Perfusion is very important in developing a suitable type of delivery device. It is necessary that the device provide a large latitude in time over which the agent could be delivered and therefore, devices which occlude blood flow may not provide the necessary latitude. Because the basic research into the biochemistry and physiologic events indicate that the initial events begin immediately after injury and continue intensely for several hours, it is desirable for the drug delivery system to allow drug delivery for several hours to a day or two beginning immediately after intervention. This research also points out that the initial events subsequently create a cascade of events that ultimately lead to intimal thickening. While these accumulations or lesions do not become apparent for several months, it is felt that if these initial events can be modulated, blocked, or even accelerated, then the subsequent cascade can be altered and a diminished overall thickening could be achieved.

Brief Summary Text (21):
It will be recognized from this discussion that there is a need for a genetic type of drug delivery system which emphasizes physician control over the device and agent. The device should have flexibility as to the agent that is to be delivered and should be capable of delivering any number of agents (either separately or at the same time), or possibly also allow a change in the protocol of the delivery. It should also be flexible with respect to the time frame over which these agents would be delivered. In order to effect this time frame of delivery, the device should also allow a large amount of blood flow by or through the device in order to maintain adequate distal perfusion of cardiac or other muscle during the delivery time.

Detailed Description Text (32):
Other embodiments of the present invention are illustrated in FIG. 4, FIG. 5, FIG. 6, and FIG. 7 with elements similar to the previous embodiment numbered similarly. FIGS. 4 and 5 illustrate this device in the blood vessel 20 both deflated (FIG. 4) and inflated (FIG. 5). As illustrated in these figures the balloons in the balloon assembly may be spaced differently and additional balloons may be placed at closer intervals. The additional balloons will aid in keeping the perfusion lumen open. The configuration and positioning of the toroidal-shaped balloons have multiple possibilities. More balloons may be formed between the previously-described toroidal-shaped balloons 10; and the balloons 12 and 16 may even be eliminated. (FIG. 7). For all of these embodiments, the distance from the most proximal balloon 16 to the most distal balloon 10 can range from about 20-30 mm and the inside balloons 10' may be disposed about 2-3 mm apart.

Detailed Description Text (33):
The number of balloons and the spacing between balloons is important in maintaining the appropriate blood flow through the vessel being treated. It is possible that the flow of blood through the sheath 22 may be cut off by any one of the following: (1) the lesion may deform the sheath; (2) the device may be placed at a bend and the sheath could kink; and/or (3) the pressure of the drug could force the blood lumen shut. Therefore, the radial support needed for the sheath 22 will vary depending on the

specific conditions of the treatment site and the particular treatment being administered. The radial support for the sheath 22 needed to maintain the blood flow lumen 24 through the center of the sheath 22 is provided by the balloons. The different configurations illustrated may be used to provide more or less radial support as needed. Increasing the number of balloons in the balloon assembly increases the ability of the balloon assembly to maintain the perfusion lumen open.

Detailed Description Text (54):
Following a typical well known PTCA procedure, the drug delivery catheter of the present invention is exchanged over the existing guide wire 34 used in the PTCA. The drug delivery catheter is slid over the guide wire 34 and positioned at the same site as the balloon dilation was performed. The balloons are then inflated to between 5 and 10 atmospheres such that the containment region is defined as explained above. Drug infusion is then initiated through the apertures in the balloon assembly to provide the desired drug to the containment pocket or region and thus to the vessel wall. The drug or agent is provided in a therapeutically effective amount and concentration for preventing aestenosis. For example, 100 mcg/ml of Heparin may be used as disclosed in "Effect of Controlled Adventitial Heparin Delivery on Smooth Muscle Cell Proliferation" by Edelman et al., Proc. Natl. Acad. Sci. (USA) 1990; 87: 3773-3778, which is incorporated herein by reference. The drug is provided at a pressure ranging from a minimal value over zero to 50 pounds per square inch (depending on the volume and concentration of drug desired). Other pressures are contemplated for other uses as per the flexible nature of this device. The blood in the vessel continues to flow through the center of the flow lumen created through the center of the balloons and the sheath. Since the flow lumen created through the center of the balloons and sheath is relatively large (compared to the size of the blood vessel), the interruption of blood flow through the blood vessel is minimized. Further, since the blood flow is isolated from the containment pocket, the drug is only administered locally and does not enter the blood stream until the balloons are deflated. This allows for the drug to be provided to the vessel wall in high concentrations without providing a high concentration of the drug in the blood stream. After the drug has been applied to the vessel wall for the desired time, the device is removed. Because of the large volume of blood flow accommodated by this invention, numerous applications of the drug may be effected without removing the drug delivery device for a relatively long period of time.

CLAIMS:

1. A blood perfusion balloon catheter comprising:

a) an elongate tubular shaft having a proximal portion and a distal portion;

b) a plurality of toroidal-shaped inflatable balloons laced through the distal portion of the tubular shaft, the balloons creating a blood flow lumen when in the inflated state; and

c) an inflation lumen in fluid communication with the inflatable balloons for inflating the inflatable balloons.

2. A blood perfusion balloon catheter for insertion into a vessel comprising:

a) an elongate tubular member having a proximal end and a distal end;

b) a toroidal-shaped inflatable balloon assembly laced through the distal end of the tubular member, the balloon assembly including a plurality of toroidal-shaped inflatable balloon members having an uninflated state and an inflated state;

the balloon assembly configured such that 1) when the balloon member is in an uninflated state, the blood in the vessel may flow around the balloon assembly, and 2) when the balloon members are in an inflated state, a flow lumen is defined through the balloon members to allow the blood to flow through the balloon members; and

c) an inflation lumen in fluid communication with the balloon members for inflating the balloon members.

3. The blood perfusion balloon catheter of claim 2 further comprising a guide wire lumen for receiving a guide wire.

4. The blood perfusion balloon catheter of claim 3 wherein the flow lumen is of a

greater diameter than the guide wire lumen.

5. A blood perfusion catheter for insertion into a vessel comprising:

a) an elongate tubular shaft having a distal end and a proximal end;

b) a balloon assembly comprising a plurality of inflatable toroidal-shaped balloons laced through the distal end of the tubular shaft and a sheath attached to the toroidal shaped balloons, the balloon assembly configured such that when the toroidal shaped balloons are inflated, the sheath forms a flow lumen allowing for blood to flow through the inflated balloon assembly; and

c) an inflation lumen in the tubular shaft in fluid communication with the toroidal-shaped balloons.

6. The blood perfusion catheter of claim 5 wherein the sheath is cylindrical.

7. The blood perfusion balloon catheter of claim 5 wherein the guide wire lumen runs substantially coaxially through the length of the tubular member.

8. The blood perfusion catheter of claim 5 wherein the sheath is attached to the torodial-shaped balloons at a section of the toroidal-shaped balloons that is radially inward of the outer diameter of the toroidal-shaped balloons.

9. A blood perfusion catheter for insertion into a vessel comprising:

a) an elongate tubular member having a proximal end and a distal end;

b) an inflatable balloon assembly disposed at the distal end of the tubular member, the balloon assembly including an inflatable balloon member having an uninflated state and an inflated state;

the balloon assembly configured such that 1) when the balloon member is in an uninflated state, the blood in the vessel may flow around the balloon assembly, and 2) when the balloon member is in an inflated state, a flow lumen is defined through the balloon member to allow the blood to flow through the balloon member; and

c) an inflation lumen in fluid communication with the balloon member for inflating the balloon member;

the balloon assembly comprising a first toroidal balloon, a second toroidal balloon disposed distally of the first toroidal balloon, additional toroidal balloons disposed between the first and second toroidal balloons, and a cylindrical sheath connected between the first and second toroidal balloons, wherein the flow lumen is defined through the center of the cylindrical sheath and the first and second toroidal balloons are in fluid communication with each other.

10. The blood perfusion catheter of claim 9 wherein the diameter of the sheath is less than the diameter of the toroidal balloons.

L8: Entry 120 of 142 File: USPT Aug 26, 1997

DOCUMENT-IDENTIFIER: US 5660855 A
TITLE: Lipid constructs for targeting to vascular smooth muscle tissue

Detailed Description Text (20):
At thirty minutes the liposomes were accumulated under the adventitia. At four hours, the liposomes began to distribute in the medial layer. At twenty-four hours, the liposomes were distributed in a heavy homogeneous pattern throughout the width of the arterial wall. At one week, the intima remained stained and the liposomes were redistributed into the adventia with the media being clear. The blood vessels of rabbits are somewhat peculiar in that the intima is extremely thin. Therefore, any intima seen after catheterization is assumed to be neointima, formed as a result of migration of VSMC from the media and consequent release of extracellular matrix. By 24 hours, the liposomes redistribute throughout the vessel. At one week the fluorescent dye is clearly seen within the neointima and not the media. Liposomes associated with VSMC within the media migrated across the internal elastica into the neointima.

Detailed Description Text (45):
A No. 2 French Fogarty catheter was used to induce vascular injury in male Spraque-Dawley rats. The rats were anesthetized, and a cannula introduced into the left common carotid via the external carotid artery. After vascular injury of the common carotid, the distal injured segment was transiently isolated by temporary ligatures. The formulation (0.25 ml) containing the antisense oligos (5 .mu.M of each) was infused into the segment and incubated for 15-30 minutes at room temperature. Control rats received an identical formulation containing reverse antisense oligos (rev-AS). Following incubation, the infusion cannula was removed and blood flow to the common carotid restored by release of the ligatures. At 2 weeks after catheterization, rats were s sacrificed and vessels perfused-fixed with 4% paraformaldehyde. Sections were analyzed for neointima formation, and data expressed as neointimal/medial area ratios and percent inhibition.

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L8: Entry 140 of 142 File: USPT Mar 19, 1974

DOCUMENT-IDENTIFIER: US 3797485 A
TITLE: NOVEL DRUG DELIVERY DEVICE FOR ADMINISTERING DRUG INTO BLOOD CIRCULATION IN BLOOD VESSEL

Abstract Text (1):
A novel drug delivery device for administering a drug into the blood circulation comprising a means for positioning a drug supply on the adventitial surface of an intact blood vessel for diffusing the drug into the blood in the blood vessel.

Brief Summary Text (2):
The present invention relates to a novel article of manufacture and to a method for using the article. More particularly, the invention pertains to a device for administering a drug into the blood circulation by diffusing the drug from the device on the adventitial surface of a blood vessel; and, to a method for administering a drug into the blood circulation by positioning a drug delivery device containing a drug on the adventitial surface of a blood vessel to diffuse the drug through the blood vessel wall into the circulating blood to produce either a localized or systemic pharmacological or physiological effect.

Brief Summary Text (21):
Another object of the present invention is to provide a method for administering therapeutically active materials for establishing therapeutically effective concentrations of the material in the blood by applying to the adventitial surface of a blood vessel a drug delivery device for diffusively administering the material into the blood.

Brief Summary Text (24):
The invention concerns a novel and useful drug delivery device for administering a drug into the blood. The drug delivery device also serves as a reservoir for at least one drug. The device comprises a means contacting a part or the whole circumference of the adventitial surface of a blood vessel for administering a drug into the blood. The invention also concerns a method for administering a drug into the blood to produce a systemic or localized effect by positioning a drug delivery device on a part or the whole adventitial surface of a blood vessel for diffusing the drug into the blood.

Detailed Description Text (4):
FIG. 2 is a cross-sectional view through 2--2 of FIG. 1 wherein device 10 at its tapered ends 13 engages blood vessel 11. In FIG. 2, body wall 12 of device 10 surrounds the adventitial surface 19 of blood vessel 11 to form at interface 17, by sealingly closing wall 12, an integral device 10. The cross-sectional view also shows intimal surface 15 defining lumen 16 of blood vessel 11.

Detailed Description Text (5):
FIG. 3 is a cross-sectional view through 3--3 of FIG. 1 illustrating device 10 with its wall 12 surrounding blood vessel 11 to form a sealed, closed device at interface 17. Drugs, not shown, in space 18 defined by the outer surface of blood vessel 11 and the inner surface of wall 12 diffuse through the adventitial surface 19 and intimal surface 15 into blood in lumen 16 of blood vessel 11. In accompanying FIG. 4 there is illustrated another cross-sectional view of device 10 of FIG. 1 surrounding blood vessel 11 before wall 12 closes to form device 10. The wall surrounds blood vessel 11 to meet at its interface 17 as seen in FIGS. 2 and 3 to form device 10.

Detailed Description Text (7):
Turning to FIG. 8, there is illustrated a drug delivery device fabricated according to the invention for engaging at least a part of blood vessel. The drug delivery device 10

of FIG. 8 comprises a body wall 12 which surrounds a part of the circumferential traverse surface of blood vessel 11. In FIG. 8, a part of the blood vessel is illustrated as surrounded and part not surrounded by device 10. The device is also constructed with inlet-outlet ports 14 that it may optionally house an in-line bacterial filter, not shown, and be filled and drained via transcutaneous tubes. The device may have a rate controlling membrane, not shown in FIG. 8. FIG. 9 illustrates a cross-sectional view through 10--10 of FIG. 8 depicting a part of a blood vessel 11 partially surrounded or saddled by device 10 comprised of wall 12 and an inner rate controlling membrane 20 prior to the closing of the device. The device of FIG. 9 can be closed by a membrane that joins the device to the artery or vein; or the device can be made with an inwardly curving wall and membrane to intimately contact the adventitial wall for sealing thereto. FIG. 10 illustrates the device of FIG. 8 positioned on blood vessel 11 in a closed or saddled engagement of 11. FIG. 11 is a top elevational view of another embodiment of the invention illustrating a small device 10 with a body wall 12 with inlet-outlet ports 14 staddled on a part of blood vessel 11, for diffusing a drug into a small area of 11. FIG. 12 is still another embodiment of the invention depicting a device 10 with a body wall 12 wrapped around a blood vessel 11 in spiral or helix arrangement for diffusing drugs into blood in 11. This device can be used for diffusing a drug over a small or a large area of blood vessel. FIG. 13 illustrates a device 10 having a body wall 12 surrounding blood vessel 11. This device is similar to the device of FIG. 12 and it can be used for contacting a large area of a blood vessel in a small space for diffusing a drug into the bloodstream.

Detailed Description Text (17):
The membrane can be formed by molding onto the device containing the drug, or the membrane can also be in the form of sheets of polymeric material permeable to the passage of the drug. The membrane can be placed at different positions from the inner surface of wall 12, or it can be laminated, adhesively affixed and the like, thereto. In spiral type devices the device is composed of an outer low permeability polymer with a rate controlled membrane joined thereto. The rate controlling membrane surrounding and contacting the adventitial surface of the blood vessel.

Detailed Description Text (54):
The drug delivery device can be used by the medical and the veterinary arts in a variety of ways. For example, the delivery device can be applied to the portal vein for the direct delivery of a drug to a target organ, the liver. The delivery device can be placed on the carotid artery for administering drugs to the brain for the management of Parkinson disease. The delivery device can also be used for the delivery of any material for systemic or regional administration, for any material indicated for local administration to an organ, for the delivery of medications for local perfusion in malignancy of an extremity and the like. The drug delivery device can be used as an internal drug reservoir, and its ports can be employed for refilling the device from an external reservoir supplying predetermined quantities of a medication to an artery or vein.

CLAIMS:

1. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising a hollow, elongate, bulbous tubule member tapered at its ends and having interior and exterior wall surfaces adapted to sealingly circumferentially engage the adventitial surface of a blood vessel longitudinally extending therethrough at both the proximal and distal ends thereof to form a pair of well-defined sealed interfaces therewith, and defining reservoir means for confining a drug supply in an annular interspace between the interior wall surface of said tubule member and the exterior wall of such blood vessel, said tubule member being provided with both inlet means and outlet means for filling and emptying the interspace, and the said tubule member being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

2. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising an elongate first tubule member having interior and exterior wall surfaces adapted to circumferentially engage the adventitial surface of a blood vessel longitudinally extending therethrough at both the proximal and distal ends thereof; a second tubule member having interior and exterior wall surfaces concentrically disposed within said first tubule member, comprising drug release rate controlling membrane, and sealingly circumferentially affixed to said first tubule member at the proximal and distal ends

thereof and adapted to longitudinally extend therethrough closely adjacent the adventitial surface of the blood vessel; the interior walls of said first tubule member defining a sealed, annular interspace for confining a drug supply, said first tubule member being provided with both inlet means and outlet means for filling and emptying the interspace; and the said first tubule member being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom through the membrane and to and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

3. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising a hollow, elongate tubule member having interior and exterior wall surfaces and circumferentially inwardly descending skirt members integral therewith and annularly depending therefrom at both the proximal and distal ends thereof, said skirt members adapted to sealingly circumferentially engage the adventitial surface of a blood vessel longitudinally extending through the tubule member to form a pair of well-defined sealed circumferential interfaces therewith, and said tubule member and skirt members depending therefrom defining reservoir means for confining a drug supply in an annular interspace between the interior wall surface of said tubule member and the exterior wall of such blood vessel, said tubule member being provided with both inlet means and outlet means for filling and emptying the interspace, and the said tubule member and skirt members being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

4. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising a hollow, elongate first tubule member having interior and exterior wall surfaces and circumferentially inwardly depending skirt members integral therewith and annularly depending therefrom at both the proximal and distal ends thereof, said skirt members adapted to sealingly circumferentially engage the adventitial surface of a blood vessel longitudinally extending through the tubule member to form a pair of well-defined sealed circumferential interfaces therewith; a second tubule member having interior and exterior wall surfaces concentrically disposed within said first tubule member, comprising drug release rate controlling membrane, and sealingly circumferentially affixed to the skirt members annularly depending from the said first tubule member and adapted to longitudinally extend therethrough closely adjacent the adventitial surface of the blood vessel; the interior walls of said first tubule member and of the skirt members depending therefrom and the exterior walls of said second tubule member defining a sealed interspace for confining a drug supply, said first tubule member being provided with both inlet means and outlet means for filling and emptying the interspace; and the said first tubule member and the skirt members depending therefrom being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom through the membrane and to and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

5. A drug delivery device for directly diffusively administering a drug into the blood through the walls of an intact blood vessel confining the same, comprising a first saddle member having interior and exterior wall surfaces adapted to sealingly engage the adventitial surface of a blood vessel longitudinally extending thereunder completely about the periphery thereof to form a well-defined, sealed, continuous peripheral interface therewith; a second saddle member having interior and exterior wall surfaces disposed beneath said first saddle member, comprising drug release rate controlling membrane, and sealingly continuously peripherally affixed to said first saddle member and adapted to extend thereunder closely adjacent the adventitial surface of the blood vessel; the interior walls of said first saddle member and the exterior walls of said second saddle member defining a sealed interspace for confining a drug supply, said first saddle member being provided with both inlet means and outlet means for filling and emptying the interspace; and the said first saddle member being essentially impermeable to the drug and body fluid, whereby, in vivo, and confining a drug supply, the drug diffuses therefrom through the membrane and to and through the walls of the intact blood vessel directly into the blood circulation in the intact blood vessel.

7. The drug delivery device as defined by claim 5, wherein the first saddle member is further of a configuration adapted to helically engage the adventitial surface of the blood vessel.

9. In a process for administering a therapeutically effective amount of an acceptable drug into the blood within an intact blood vessel wherein the process comprises placing a drug delivery device adapted for supplying a drug on the adventitial surface of a blood vessel, the device comprised of a wall formed of a material essentially impermeable to drug within the wall forming a reservoir and adapted to embrace the adventitial surface of the blood vessel, a reservoir for supplying drug and defined by the inner surface of the wall, an inlet port and an outlet port connected to the reservoir for supplying drug to the reservoir, and wherein drug is released from the reservoir when charged with drug and in contact with the adventitial surface for diffusively administering the drug through the blood vessel and into the blood from the device.

12. In a process for administering a drug from a drug delivery device according to claim 9 wherein the device further comprises a drug release rate controlling membrane permeable to the passage of drug for controlling the rate of drug diffusion from the device to the adventitial surface of the blood vessel wall, said membrane positioned and joined to the edges of inner surface of the wall with the drug contained in the reservoir formed by the inner surface of the wall and the membrane.